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EXAMINER	
HIBBERT, CATHERINE S	

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1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,405	WATZELE ET AL.	
	Examiner	Art Unit	
	Catherine S. Hibbert	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 15-23* is/are pending in the application.

4a) Of the above claim(s) *11-13 and 15-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 19-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 June 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/9/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This is the First Office Action on the Merits of US Application No. 10/538,405 filed 9 June 2005, which claims priority to 371 of PCT/EP03/13964 (12/09/2003) which claims priority to Foreign Application DE102/57/479.0 filed 9 December 2002. Claims 1-13 and 15-23 are pending. Claim 14 is cancelled. Claims 11-13 and 15-18 are withdrawn. Claims 1-10 and 19-23 are under consideration in this action.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Please note that Applicant cannot rely upon the foreign priority papers to overcome a prior art rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Election/Restrictions

Applicant's election without traverse of the species "*in vitro* prokaryotic cell lysate expression system" and "cell lysate prepared from *E. coli*" in the reply filed on 21 September 2007 is acknowledged.

Claims 11-13 and 15-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species/subject matter, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 21 September 2007.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one

or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6-7 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 recites the limitation "the region of the heterologous nucleic acid sequence that is on the 5' side of the stem-loop structure" in lines 1-3. There is insufficient antecedent basis for this limitation in the claim. In addition, the claim, as written, does not require that the heterologous nucleic acid sequence contains any nucleotide sequence on the 5' side of the stem-loop structure.

Claim 7 recites the limitation "the region of the heterologous nucleic acid sequence that is on the 5' side of the stem-loop structure and on the 3' side of the start codon" in lines 1-3. There is insufficient antecedent basis for this limitation in the claim. In addition, the claim, as written, does not require that the heterologous nucleic acid sequence contains any nucleotide sequence on the 5' side of the stem-loop structure.

Claim 23 recites the limitation "the nucleic acid sequence coding for the protein" in lines 3-4. There is insufficient antecedent basis for this limitation in the claim.

Claim 23 recites the limitation "the translation start codon" in line 7. There is insufficient antecedent basis for this limitation in the claim because there can be more than one translation start codon in a nucleic acid construct.

Claim 23 recites the term "the heterologous nucleic acid sequence" in lines 4 and again in lines 5-6. The antecedent basis for the term "the heterologous nucleic acid sequence" is not clear because the claim recites, in lines 3-4, "a nucleic acid sequence that is heterologous to the nucleic acid sequence coding for the protein". Since both the "nucleic acid sequence" and the "nucleic acid sequence coding for the protein" are heterologous to each other, it is not clear to which heterologous nucleic acid the term "the heterologous nucleic acid sequence" refers.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10 and 19-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when

accompanied by a method of obtaining the claimed sequence." MPEP § 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618. The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163. While all of the factors have been considered, a sufficient amount for a *prima facie* case are discussed below.

In the instant case, the claims are drawn to a composition for producing a protein, the composition comprising a nucleic acid sequence that is heterologous to the

nucleic acid sequence coding for the protein wherein the heterologous nucleic acid is inserted into the protein-coding nucleic acid sequence in the correct reading frame and wherein the heterologous nucleic acid sequence forms a stem-loop structure 6-30 nucleotides from the 3' side of the translation start codon; and an expression system for the protein (claim 23). Claims 1-10 and 19-22 are drawn to a method for producing a protein comprising providing a nucleic acid sequence coding for the protein wherein the nucleic acid sequence coding for the protein comprises a translation start codon, inserting a heterologous nucleic acid sequence on the 3' side of the translation start codon in the correct reading frame wherein said heterologous nucleic acid sequence forms a stem-loop structure on the 3' side of the translation start codon 6-30 nucleotides from the 3' side of the start codon, introducing the combined nucleic acid sequences into an expression system for the protein, and forming the stem-loop structure wherein the length of the stem is in the range of 4-12 nucleotides.

As stated *supra*, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable that claim(s) 1-10 and 19-23 is/are broad and generic, with respect to all possible compounds encompassed by the claims. The possible structural variations are numerous to any nucleic acid sequence of any length which can form a stem-loop structure 6-30 nucleotides from the 3' side of the start codon. Even the limitations of claims 3 and 4 that require a specific length of up to 45 and 201 nucleotides for the portion of the nucleic acid sequence comprising "the heterologous nucleic acid sequence" does not rectify the problem. While the specification describes an example

of a hairpin loop and a stem length of 7 bases at a distance of 15 bases after the start codon for three introduced into the coding sequence of the three different proteins, survivin, cytomegalovirus capsid protein 1049 (1049) and Class II transactivator (CIITS), the specification does not describe a representative number of variants of this working example or a representative number of the enormous number of potential protein coding sequences for all proteins for one of skill in the art to be able to envision the structure of the next species of nucleic acid sequences that are able to function to form a stable, functional stem-loop in order to substantially prevent the formation of stable stem-loop structures in the region of the Shine-Dalgarno sequence and of the start codon and thus to effect a more efficient initiation phase of translation but conversely to form a stem-loop that is sufficiently unstable to be able to un-pair the stem-loop during the elongation phase of translation in order to produce proteins in various expression systems.

Further, the claims are drawn to a sequence, and the specification teaches a length of a sequence only for claims 3 and 4 that require a specific length of up to 45 and 201 nucleotides while claims are drawn to any length sequence (except for claims 3 and 44 that require a specific length of up to 45 and 201 nucleotides). The recitation of the stem-loop sequences in the specification does not appear to be representative of this broad genus of variants of broadly claimed sequences because the formation of secondary structures in RNA molecules, such as stem-loop structures and intra-molecular as well as intermolecular triple base interactions can be highly unpredictable and varied depending on solution conditions such as substrate concentrations and salt and pH conditions of the expression system (See Ciullo et al reference below).

Ciullo et al in "Downstream Sequence Adjacent to AUG Affects Translation of Chloramphenicol Acetyl Transferase in Eukaryotic Cells" (DNA and CELL Biology, Vol 19, 2000, p.39-46; see whole document) teach a nucleic acid sequence that is heterologous to nucleic acid sequence coding for the CAT protein wherein the nucleic acid sequence is inserted just downstream from the AUG start codon in the correct reading frame and wherein the nucleic acid forms a stem-loop structure 12-21 nucleotides from the 3' side of the translation start codon (see p.39, abstract; p.41, ¶ 1, lines 1-15). However, the prior art does not appear to offset the deficiencies in the specification in that it does not describe all the variants, or a representative number of variants, of a heterologous nucleic acid sequence that when inserted on the 3' side of the translation start codon in the correct reading frame of essentially any protein coding sequence and wherein said heterologous nucleic acid sequence forms a stem-loop structure on the 3' side of the translation start codon 6-30 nucleotides from the 3' side of the start codon, and upon introducing the combined nucleic acid sequences into an expression system for the protein, and forming the stem-loop structure wherein the length of the stem is in the range of 4-12 nucleotides results in a method for producing protein.

Therefore, there is no structural and functional basis provided by the prior art or the instant specification for one of skill in the art to envision the broad genus of variants of sequences that maintain the ability to form a stem-loop in order to enhance translation initiation without blocking translation elongation. A few examples of short nucleic acid sequences which can form stem-loops and function as insertions into three

different protein-coding sequences is not representative of the functionally different or equivalent sequences from this broad class. One of skill in the art would not have been able to envision a representative number of variations in the nucleic acid sequence of the sequences presented in the specification that function to produce proteins in an expression system. One of skill in the art would have thus reasonably concluded that the applicants were not in possession of the full breadth of the claimed invention for claims 1-10 and 19-23.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now is claimed." (See Vas-Cath at page 11 16). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation or identification. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Although the claims may recite some functional characteristics, the claims lack written description because there is insufficient disclosure of a correlation between function and structure of the compounds beyond those compounds specifically disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus. While having written description of the nucleic acid sequences listed in the specification, and compounds identified in the specification tables and/or examples, the specification does not provide sufficient descriptive support for the myriad of compounds embraced by the claims.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-10 and 19-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Ciullo et al in "Downstream Sequence Adjacent to AUG Affects Translation of Chloramphenicol Acetyl Transferase in Eukaryotic Cells" (DNA and CELL Biology, Vol 19, 2000, p.39-46; see whole document).

Ciullo et al teach a nucleic acid sequence that is heterologous to nucleic acid sequence coding for the CAT protein wherein the nucleic acid sequence is inserted just downstream from the AUG start codon in the correct reading frame and wherein the nucleic acid forms a stem-loop structure 12-21 nucleotides from the 3' side of the translation start codon (see p.39, abstract; p.41, ¶ 1, lines 1-15). In addition, Ciullo et al teach an in vitro transcription/translation expression system for the protein as well as an in vivo translation system in mammalian COS cells. In addition, Ciullo et al teach a method for introducing the nucleic acid sequences into the in vivo and/or in vitro expression systems, forming a stem-loop structure 12-21 nucleotides from the 3' side of the start codon wherein the structure "exhibits a calculated stability significantly lower than that required for a hairpin to act as an enhancer of translation in vitro" (abstract, lines 3-4) and wherein the region of the heterologous nucleic acid sequence that is on the 5' side of the stem-loop structure and on the 3' side of the start codon has a GC

content of less than 50% (see especially p. 41, Fig. & legend 1A). In addition, Ciullo et al teach recombinant nucleic acid construction by cloning and two-step polymerase chain reaction techniques (p.40, ¶ 2-4). In addition, Ciullo et al teach purification of the CAT protein by a (CAT protein purification domain) by immunosorbent and SDS PAGE techniques (p. 41, ¶ 4, lines 1-12). In addition, Ciullo et al teach where the heterologous coding sequence was codon-adapted for expression in COS-cells and for in vitro transcription/translation in the T7 prokaryotic and rabbit reticulocyte lysate systems (p. 40, right column, ¶ 4, lines 1-8). Furthermore, Ciullo et al teach wherein a heterologous nucleic acid sequence has a length of less than 45 nucleotides (see especially p. 41, Fig. & legend 1A).

Therefore, Ciullo et al reads on all of the limitations of the instant claims 1-10 and 19-23.

Claims 1-5 and 19-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Hinton et al in "Internal Ribosomal Entry Site-Mediated Translation Initiation in Equine Rhinitis A Virus: Similarities to and Differences from That of Foot-and–Mouth Disease Virus", (Journal of Virology, Vol. 74, December 2000, p.11708-11716; see whole document).

Hinton et al teach a composition for producing the two reporter proteins CAT and GFP, the composition comprising: an expression system for the protein (BHK-21 cells, p.11709, ¶ 2, line 2); and a nucleic acid sequence that is heterologous to the CAT and/or GFP sequence, wherein heterologous nucleic acid sequence is inserted into

protein-coding nucleic acid sequence in the correct reading frame and wherein heterologous nucleic acid sequence forms a stem-loop structure (e.g. N stem-loop) 6-30 nucleotides from the 3' side of an AUG translation start codon (see especially p. 11711, Figures and legends 2 and 3; p.11713-11714, Figures and legends 5A and 6A, and p.11712, ¶ 4, lines 1-6). Therefore, Hinton et al anticipate all the limitations of independent claim 23.

In addition, Hinton et al teach a method for producing the CAT and GFP proteins using the heterologous construct described above wherein the length of the stem is in the range of 4-12 nucleotides (p. 11710, N stem-loop/Figure 1) and further to isolating the protein by immunoprecipitation using rabbit anti-CAT and rabbit anti-GFP directed against the "CAT" and/or "GFP" purification domains of the heterologous nucleic acid, (p.11709, ¶ 3, lines 6-16) which meets all of the limitations of claims 1-2 and 22. For example, Hinton et al report

> a plasmid "that comprised the CAT and GFP reporter genes under the control of the T7 promoter was constructed (Fig. 2). Initially the entire 5'-NTR sequence downstream of the poly(C) tract was inserted as an intergenic spacer between the two reporter genes. The 3' boundary of this insert was placed at the 104 nt downstream of the first putative initiation codon, as this region included other potential initiation codons, as well as two further predicted stem-loops, here named M and N (Fig. 1). The GFP gene was in frame with the putative initiation codons. Inserts containing progressive 5' deletions of the ERAV 5'NTR were also inserted into the pT7CG plasmid. When transfected into BHK-21 cells infected with a recombinant vaccinia virus that expresses T7 polymerase (vTF7-3), the full-length construct pE1 (1-961) produced high levels of GFP compared to the parental plasmid" (paragraph spanning p.11710-11711).

In addition Hinton et al teach the method of claim 1 and to wherein a stem-loop structure is formed 12-21 nucleotides from the 3' side of the start codon, which meets the limitations of claim 5.

Hinton et al further teach wherein a nucleic acid sequence coding for a protein is provided by a method selected from the group consisting of cloning, recombination and amplification and further to wherein the nucleic acid sequence coding for the protein is provided by a two-step polymerase chain reaction, which reads on all the limitations of claims 19 and 20. For example, Hinton et al recite "all plasmids were constructed using standard cloning methods" (p.11709, ¶ 4, line 1) and "the 5'-NTR regions of ERAV 393/76 were subjected to reverse transcription followed by PCR amplification with specific oligonucleotides" (p.11709, ¶ 5, lines 1-2). Therefore, Hinton et al anticipates all the limitations of claims 19-20.

Hinton et al further teach wherein the nucleic acid sequence coding for the protein or the heterologous nucleic acid sequence comprises a codon adapted, based on codon usage, to the expression system, which reads on the limitations of claim 21. For example, Hinton et al recite "the major FMDV initiation codon is the second of two utilized AUG codons, which, unlike AUG1, is in an optimal Kozak context. We constructed a plasmid, pE1(245-961)A2con, that mimics the FMDV AUG1 context." Therefore, Hinton et al anticipate all the limitations of claim 21.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hinton et al as applied to claim 1 above, and further in view of Pavlov & Ehrenberg

in "Rate of Translation of Natural mRNAs in an Optimized In Vitro System", (Archives of Biochemistry and Biophysics, Vol.328, p.9-16, 1996).

Claims 8-10 are directed to the method of claim 1 (described above) and further to wherein a prokaryotic in vitro expression system comprising a lysate of *Escherichia coli* is used.

Claim 1 is taught by Hinton et al for the reasons described above.

However, Hinton et al. differs from the invention claimed in the instant claims 8-10 in that while it teaches an in vivo protein expression system such as the transient transfection of mammalian BHK-21 cells in culture, Hinton et al. fails to teach the use of an E. coli in vitro translation system.

Pavlov & Ehrenberg teach a prokaryotic in vitro expression system comprising a lysate of *Escherichia coli* (p.10, ¶ 2, lines1-9 and ¶ 3, lines1-10). It would have been obvious to one of ordinary skill in the art at the time the invention was made to have utilized E.coli lysate expression system of Pavlov & Ehrenberg in the method taught in Hinton *et al.* because Pavlov & Ehrenberg teach that the E.coli in vitro translation systems were successfully used, were available, and were often routine at the time of the instant invention (p.9, ¶ 1, lines1-6).

One would have been motivated at the time the invention was made to have utilized the E. coli in vitro translation system in the method of Hinton *et al.* because Pavlov & Ehrenberg recite "one purpose of the present work is to make possible the study of important aspects of protein synthesis that are out of reach with homopolymeric mRNAs and that so far have been studied with suboptimal systems. Another aim is

large-scale and accurate in vitro production of important proteins that cannot easily be expressed in vivo. A third goal is to make possible in vitro engineering of proteins , which cannot be carried out in vivo" (p.9, ¶ 2, lines1-9). Pavlov and Ehrenberg also recite "we present data from an in vitro translation system in which optimal properties of the polymix buffer have been combined with translation of natural mRNAs. We have used an mRNA transcribed in vitro from the tufB gene of Escherichia coli. This mRNA coding for elongation factor Tu (TuB) has a codon bias typical for highly expressed genes and may therefore be optimal for fast translation"(p.9, ¶ 3-4). In addition, both Hinton *et al.* and Pavlov & Ehrenberg are in the same field of endeavor (expression of recombinant proteins) and both are directed to the same problem sought to be solved (optimization of production of recombinant proteins).

Absent evidence to the contrary, one would have a reasonable expectation of success combining the teachings of the art because the use of the an E.coli in vitro translation system for the purpose of expressing recombinant proteins was routinely practiced at the time the teachings of Hinton *et al.*, and Pavlov & Ehrenberg were published.

In view of the foregoing, the method of claims 1 and 8-10, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC *§103(a)*.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Catherine S. Hibbert whose telephone number is 571-270-3053. The examiner can normally be reached on Monday-Friday, 7:30 AM-5:00 PM, ALT. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully submitted,

Catherine S. Hibbert/AU1636